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Original Research Article

Evaluation of clinical efficacy and safety of natural micronized progesterone in prevention of preterm labor: a prospective study at tertiary care teaching hospital in India

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ABSTRACT

Background: Uterine relaxants (UR) are used in management of in Preterm labour (PTL), which is responsible for considerable morbidity and mortality in mother as well as preterm infant. Author are yet to discover an ideal UR which is highly effective yet safe. Literature supports the use of natural micronized progesterone (NP) during threatened PTL. However, little data exists for Indian population. Therefore, present study becomes imperative.
Methods: A comparative clinical study was carried out on 78 patients (aged 19 to 35 years with singleton pregnancy and gestational age between 28 and 37 weeks with cervix ≤4 cm dilated) who were diagnosed with threatened PTL were included. Those who refused treatment were allocated to control group (n= 29) and received only bed rest. NP was given orally 200 mg twice a day to 21 patients and 200 mg intra vaginal twice a day to 28 patients and was continued until delivery or 37 weeks of gestation whichever occurred first. The efficacy was proven if PTL was prevented and patient did not require an alternative UR for ≥48 hours.
Results: The mean age of patients was 23±3.2 years, majority being multipara. Author observed that both oral and vaginal formulation of NP was found to be highly effective ($p < 0.05$) as primary UR and maintenance therapy in preventing PTL as compared to the control group. However, difference between them was not statistically significant. None of the patients were lost to follow-up and no adverse events linked to the treatment were reported.
Conclusions: Although, the data obtained from this study was limited and the sample size was small, findings of this study support the use of NP in prolonging threatened PTL.

Keywords: Preterm labour, Progesterone in preterm labour, Tocolytics

INTRODUCTION

Uterine relaxants or tocolytics are the drugs used to suppress premature uterine contractions. Preterm labour (PTL) is responsible for preterm birth. Babies born alive and delivered between 28-37 completed weeks of gestation are referred to as preterm babies.[1] According to WHO, every year an estimated 15 million babies are born preterm and India is ranking first with greatest number of preterm births. It is leading cause of death among children

under 5 years of age, responsible for approximately 1 million deaths in 2015.[2] PTL is associated with poor neonatal outcomes like respiratory distress syndrome, intraventricular hemorrhage, patent ductus arteriosis, jaundice, anemia, necrotizing enterocolitis, bronchopulmonary dysplasia and poor maternal outcomes.[3]

Patients who need transfer to a hospital which can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids are primary beneficiaries from use of a tocolytic agent.[4] Currently used tocolytics are β sympathomimetics (ritrodrine, isoxsuprine and salbutamol), calcium channel blockers, atosiban, nitric oxide donors like glyceryltrinitrate, magnesium sulphate and progesterone.[5] Many trials are underway to select an ideal tocolytic which is highly effective yet produces toxicity to baby and the mother.

Recent literature supports the use of natural micronized progesterone (available in oral and vaginal dosage forms) as tocolytic agent, prophylactic and as maintenance therapy during threatened preterm birth because it decreases several complications of prematurity such as respiratory distress syndrome.[6] However, no formal evaluation of its efficacy and safety has been carried out in Indian population. Author conducted this study to assess the effectiveness of oral as well as vaginal progesterone in prolonging the threatened PTL for ≥48 hours and to analyse the maternal and fetal outcomes associated with it.

METHODS

This comparative clinical study was carried out in the Department of Obstetrics and Gynecology of a tertiary care teaching hospital in Western India from April 2018 to July 2018. The study began obtaining permission from institutional review board and informed consent was provided by all the participants. A total of 78 patients diagnosed with threatened PTL and aged between 19 to 35 years with singleton pregnancy of gestational age between 28 and 37 weeks from last menstrual period and cervix no more than 4 cm dilated were included. Patients with severe pre-eclampsia, eclampsia, multiple gestation and premature rupture of membrane, hypotension, cardiac disease, chorioamnionitis and congenital fetal malformation, non-reassuring fetal heart rate and abruption placentae were excluded. The selected patients who refused treatment were allocated to control group (n= 29). Rest were divided into group 1 (n= 21) and group 2 (n=28) by using lottery method. Patients in control group received no medication, they were given only reassurance and bed rest. Natural micronized progesterone was given orally 200 mg twice a day in group 1 and 200 mg intra vaginal twice a day in group 2. Progesterone was continued in group 1 and 2 until delivery or 37 weeks of gestation whichever occurred first. All the patients also received a course of betamethasone, consisting of two 12 mg injections intravenously during the first 24 hours after admission. The primary outcome i.e. efficacy was assessed if PTL was prevented and woman with PTL did not require an alternative tocolysis for ≥48 hours. Maternal and neonatal outcomes were additionally recorded and analysed. Data was analyzed with statistical analysis program (SPSS version 23). Numerical variables were presented in the form of mean ±SD. Fischer's exact test was applied to evaluate primary outcome. Student's unpaired t-test was applied to analyse quantitative variables. P value equal or less than 0.05 was considered as statistically significant.

RESULTS

Maternal age at the time of presentation ranged from 19 to 35 years with mean age of 23±3.2 years (control group- 23±3.1, group 1- 22.2±2.4, group 2- 23.4±3.9), majority being less than 25 years of age. Gestational age at the time of diagnosis varied from 28 to 36 weeks (calculated from last menstrual period) as illustrated in Figure 1. Two patients in control group and 1 patient each in group 1 and group 2 were primi-gravida, rest all were multipara. All three groups were not statistically different in these demographic measures. None of the patients were lost to follow-up and no adverse events linked to the treatment were reported.

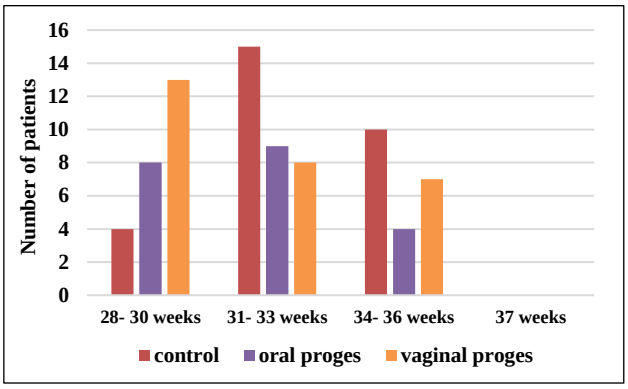

Figure 1: Gestational age at the diagnosis of PTL.

Efficacy measure

Out of a total 78 patients, primary outcome was achieved in 39 patients (50%). Refer Figure 2.

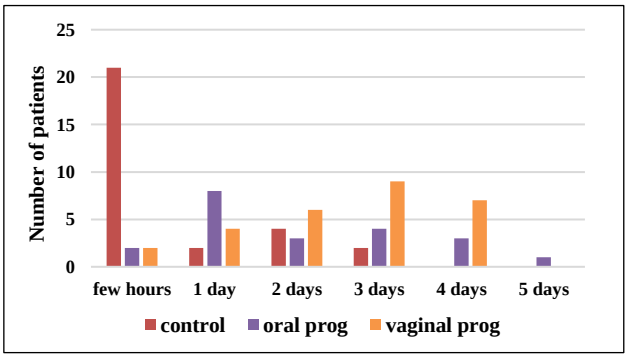

Figure 2: Serum creatinine before surgery.

PTL was prevented by ≥48 hours in 20.6%, 52.3% and 78.5% of patients in control, group 1 and group 2 respectively. A significant difference in efficacy was found when control group was compared with group 1 (p=0.03) and group 2 (p=0.0001). However, the difference was not statistically significant between group 1 and group 2 (p=0.06). PTL was not prolonged for >5 days in any of the patients.

Maternal outcome

The percentage of women who delivered by cesarean section was higher in group 2 (41%) as compared to control group (38%) and group 1 (21%). Post-partum hemorrhage (PPH), followed by anemia and vaginal infection was the most common adverse maternal outcomes as summarized in Table 1.

Table 1: Adverse maternal outcome.

Adverse maternal outcome	Control group	Group 1	Group 2	Total
PPH	8	3	4	15
Anemia	5	2	6	13
Vaginal infection	6	4	0	10
Low platelets	1	0	1	2
Breathlessness	1	0	0	1

Neonatal outcome

Only 10.2% of the neonates delivered in this study had birth weight ≥2.5 kg. Thus, low birth weight was the most common adverse neonatal outcome. Mean birth weight of the neonates was 1.72±0.5 kg (control group- 1.6±0.4, group 1- 1.7±0.3, group 2- 1.8±0.4), the difference in birth weight being non-significant across the groups (p >0.05).

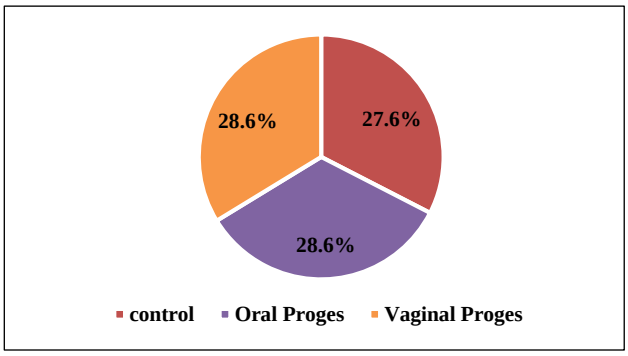

Figure 3: Respiratory distress in neonates born to mothers diagnosed with PTL.

More than half of the neonates (58.9%) required admission in NICU (control-65.5%, group 1-66.7% and group 2-46.4%), the difference between the groups being non-significant (p >0.05). The number of days of NICU stay varied between 2 to 8 days, mean±SD=2±1.9 days (control-2±2 days, group 1-1.5±1.7 days and group 2-2.3±2 days). There was no significant difference between the groups (p >0.05). Respiratory distress (Figure 3) was the next most common finding, hence 28.2% neonates in this study needed the use of surfactant and the difference between the groups was not significant (p >0.05). Other less common outcomes were anemia (7.6%) and infection (7.6%). No cases of neonatal intraventricular hemorrhage, necrotizing enterocolitis or congenital malformation occurred.

DISCUSSION

Despite the recent advances in knowledge, PTL continues to have high incidence in Indian population. It is imperative to diagnose PTL and intervene so as to prolong delivery by at least 48 hours. Buying this time help steroids to aid in fetal lung maturity and to transfer the patient to a center where neonatal care facilities exists. There is a growing body of evidence that supports the use of natural micronized progesterone for prevention as well as treatment of PTL. We evaluated this by using two formulations i.e. oral and vaginal and compared it with conservative treatment i.e. reassurance and bed rest. To the best of our knowledge, this study is the first of its kind in India.

The mean age of women in this study was 23±3.2 years. Gestational age at the time of diagnosis varied from 28 to 36 weeks. In this study, PTL was prevented by ≥48 hours in 20.6%, 52.3% and 78.5% of patients in control, group 1 and group 2 respectively. Author observed that both oral and vaginal formulation of natural micronized progesterone was found to be highly effective as primary tocolytic agent and maintenance therapy in preventing PTL as compared to the control group. However, difference between oral and vaginal formulations was not statistically significant.

Present results are in line with one of the pioneer study which found that acute tocolytic effect of oral micronized natural progesterone on uterine contractions was statistically significant as compared to the ritrodrine.[7] In yet another study, authors found that treatment with oral micronized natural progesterone did not prolong pregnancy but the total tocolytic dose of betamimetics and length of hospital stay were reduced in the micronized natural progesterone treatment group.[8]

Additionally, study from Turkey documented that micronized natural progesterone therapy if continued as a maintenance treatment until delivery (or 37 weeks of gestation), can significantly delay delivery and reduce incidence of low birth weight babies.[9] A similar trial was conducted using 100 mg of intravaginal micronized natural progesterone in high-risk pregnant women, which reported that prophylactic vaginal micronized natural progesterone reduced the rate of preterm birth, although no information was provided about perinatal outcomes.[10] In this study, neonatal outcomes such as birth weight, need of NICU stay, length of NICU stay, respiratory distress and need of

surfactant were not statistically different between progesterone and control group. Present findings are in contrast with the previous work done by Borna S et al, who reported a significant decrease in respiratory distress syndrome among infants whose mothers received micronized natural progesterone maintenance therapy.[11] However, it is meaningful to note that authors in that study had used 400 mg of micronized natural progesterone and therapy had commenced after discontinuation of the other tocolytic treatment, which differs from the methods used in this current study (author have used micronized natural progesterone for both tocolytic and maintenance treatment). One such study which evaluated the prophylactic effect of micronized natural progesterone in women with shortened cervix in mid-trimester and it was concluded that progesterone reduces the rate of spontaneous early preterm birth but did not result in any significant improvement in neonatal mortality, similar to the results reported here.[12]

CONCLUSION

Although, the data obtained from this current study is limited and the sample size is small, findings of this study support the use of natural micronized progesterone in prolonging threatened preterm labour.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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